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Bone Marrow Transplantation Versus Chemotherapy for Maintenance of Second Remission of Childhood Acute Lymphoblastic Leukemia: A Study of the Children's Cancer Group (CCG-1884)

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Background. Maintenance of second remission of childhood acute lymphoblastic leukemia (ALL) with intensive chemotherapy is often unsuccessful. The major cause of treatment failure is relapse.

Materials and Methods. Of 96 children with ALL who relapsed in the marrow while on or within 1 year of completing initial therapy, 62 achieved a second remission. Nineteen patients underwent bone marrow transplantation in second remission, 11 from a human leukocyte antigen (HLA)-matched related donor, seven using autologous marrow, and one from a matched unrelated donor. The event-free survival (EFS) of transplanted patients was compared to that of patients treated with intensive chemotherapy using high-dose cytarabine, vincristine, escalating dose methotrexate, L-asparaginase, and an anthracycline (daunorubicin or idarubicin). Only those patients treated with chemotherapy who survived in second remission up to the mean time that patients were transplanted (135 days) were included in the control group (33 of 43 patients who achieved second remission).

Results. The actuarial 2-year event-free survival of transplanted patients is 37 ± 22% (95% C.I.) compared to 18 ± 13% for chemotherapy-treated patients (P = 0.017). EFS for allo-transplant recipients was similar to that for auto-transplant recipients. Duration of initial remission was a strong predictor of the outcome of retrieval therapy. Patients whose initial remission was greater than 3 years had better EFS after achieving second remission (five of 11 still in remission, compared to four of 41 patients whose initial remission was less than 3 years). Adjustment in the multivariate analysis for duration of initial remission did not diminish the benefit of transplant over chemotherapy.

Conclusions. While there remains considerable possibility for further improvement in EFS after achieving second remission of childhood ALL, bone marrow transplant is superior to chemotherapy in maintaining second remission. Med. Pediatr. Oncol. 29:534–540, 1997.

Key words: childhood acute lymphoblastic leukemia; bone marrow transplant; chemotherapy

INTRODUCTION

The outcome of retrieval therapy for children with acute lymphoblastic leukemia (ALL) who relapse in the bone marrow is inadequate and fundamental strategies to manage these patients remain a topic of controversy. While second remissions can be obtained in most of these children with standard chemotherapy, the achievement of satisfactory long-term disease-free survival remains an elusive goal. The Berlin-Frankfurt-Munster (BFM) group has reported 6-year event-free survival of 31% for children treated with an intensive chemotherapeutic regimen after initial hematologic relapse [1]. This result is remarkable in light of the aggressive nature of the unsuccessful primary treatment these children had received, but is not substantially different from the outcome of a previously reported Pediatric Oncology Group (POG) study [2].

Several studies have suggested a potential role for allogeneic bone marrow transplantation for children with ALL who enter a second remission after hematologic relapse [3–9]. While some of these studies have been criticized for patient selection bias and waiting time bias [10–12], one of the main problems of allogeneic transplantation that limits its application is the lack of a suitably matched donor. As an alternative to matched marrow transplants from related donors, some investigators have studied the role of autologous transplantation [13–15] and, while treatment-related morbidity is low, relapse remains a major problem. Conversely, with the use of transplants from unrelated donors [16–20] and mismatched related donors [21,22], treatment-related morbidity and mortality, especially graft-versus-host disease

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(GVHD), are significant factors in diminishing the quality and duration of survival.

Thus, the role of transplantation in the management of childhood ALL remains a matter of scrutiny. In this report, we present data comparing the outcome of transplantation to chemotherapy in a cohort of 62 children with ALL who achieved second remission after a hematologic relapse.

MATERIALS AND METHODS

Patient Population

Eligibility for entry on this study (CCG-1884) required that children with ALL had relapsed while on therapy or within 1 year of completion of primary therapy. Patients with only extramedullary relapse were excluded, as were patients who had received more than 300 mg/m^2 prior anthracycline and children with substantial functional impairment of major organs. It was required that patients be less than 21 years of age at original diagnosis and over 1 year of age at the time of entry onto this study. Informed consent was required according to the policies of individual institutions as approved by the Department of Health and Human Services.

Sixty-two of 96 entered patients achieved second remission. Among these second remission patients, 11 had an HLA-A, -B, and -DR matched related donor and underwent allogeneic marrow transplant at a mean of 124 days (range:69–250) after achieving second remission. There were no patients reported to have a matched related donor who achieved a second remission, but were not transplanted.

Seven patients underwent autologous bone marrow transplantation at a mean of 143 days (range:69–323) after achieving second remission. A single patient underwent a matched unrelated marrow transplant 190 days after achieving second remission. The decision to offer an autologous or unrelated marrow transplant was done by institutional choice. Overall, the mean time to transplantation was 135 days (median = 101 days; range = 66–323 days).

There were 43 patients treated with maintenance chemotherapy. Among these, 10 patients relapsed prior to 135 days after the achievement of second remission, the mean time to transplant for patients undergoing bone marrow transplant (BMT).

The patient populations were compared for characteristics which might be considered to be of prognostic significance for relapse. The factors analyzed were WBC at diagnosis, age at diagnosis, duration of initial remission, ethnicity, CD10 immunophenotype, gender, and the intensity of prior therapy. No significant differences were observed when transplanted patients were compared to patients treated with maintenance chemotherapy (Table I).

TABLE I. Patient Characteristics

	Number		
	BMT	CHEMO	*P*
	19	33	
WBC at diagnosis			
<10,000	12	25	
10,000–50,000	4	7	0.24
>50,000	3	1	
Age at diagnosis (yrs)			
<4	4	3	
4–9	12	19	0.26
⩾10	3	11	
Duration of CR1 (mos)			
<12	5	5	
12–36	9	21	0.43
>36	5	6	
Not available		1	
Ethnicity			
Caucasian	13	21	
Other	6	12	0.96
CD10 Immunophenotype			
Positive	15	19	
Negative	4	6	0.89
Not available		8	
Gender			
Female	13	15	
Male	6	18	0.19
Prior therapy			
Standard	2	6	
Intensive	17	27	0.73

Treatment Plan

Patients received reinduction therapy with vincristine (VCR), prednisone (P), L-asparaginase (L-ASP), and an anthracycline, either daunorubicin (DNR) or idarubicin (IDR), the choice made by randomization. Central nervous system (CNS) therapy used cytarabine (ARA-C) and hydrocortisone in age-appropriate doses. Details of the induction therapy used have been previously reported [23].

Those patients achieving second remission were treated with an interim maintenance therapy of VCR, methotrexate (MTX), and L-ASP, as described by Capizzi [24]. The purpose of this therapy was to provide a respite from intensive induction, during which the availability of a suitable marrow donor could be assessed and a decision regarding transplantation could be made. Two or three cycles of interim therapy were given at 10 to 14-day intervals as clinically tolerated before definitive maintenance chemotherapy was begun.

Maintenance chemotherapy consisted of repeated cycles of chemotherapy with a modified regimen of high-dose ARA-C with L-asparaginase [25], combined with the same anthracycline used in induction, followed by four cycles of escalating dose MTX as described by Capizzi [24]. The schedule and details of dosage have been previously reported [23]. The overall five-phase

TABLE II. BMT Conditioning Regimens

	Number
Allogeneic	
Conditioning regimens	
ARA-C/FTBI[a]	6
CTX/FTBI	4
BU/CTX[a]	1
GVHD prophylaxis	
CSA/MTX[a]	4
CSA/steroid	2
MTX	2
CSA	1
CSA/MTX/steroid	1
None	1
Autologous	
Conditioning regimens	
CTX/FTBI	5
BU/CTX	1
CTX/VERAPAMIL	1
Purging procedures	
Chemotherapy	3
Chemo/immunotoxin	2
Monoclonal antibodies/complement	1
None	1
Unrelated donor	
Conditioning regimen	
CTX/FTBI	1
GVHD prophylaxis	
CSA/steroids	1

[a]Ara-C, cytarabine; FTBI, fractionated total body irradiation; CTX, cyclophosphamide; BU, busulfan; CSA, cyclosporine-A; MTX, methotrexate.

cycle was repeated approximately every 10–12 weeks as tolerated for 2½ years or until the patient relapsed.

Eleven patients with an HLA-matched related donor were treated with allogeneic bone marrow transplant. The conditioning regimens and graft-versus-host disease prophylaxis were done according to protocols established at the transplant institutions. Seven patients received autologous transplants. Six of the autologous marrows used were purged by chemotherapeutic or immunologic procedures. Autologous transplant recipients received no graft-versus-host prophylaxis. A single patient received a marrow transplant from an HLA-matched unrelated donor. The conditioning regimens and graft-versus-host prophylaxis used are listed in Table II.

Statistical Methods

Since analysis of the effect of BMT outcome can be subject to numerous biases, including the waiting time effect [26], two approaches were used to try to adjust for this problem. The first approach uses the landmark method [27] which examines the outcome of each BMT patient from the time of that patient's transplant. The comparison ''control'' group (33 patients) consists of a subset of patients who did not receive BMT, but had an event-free survival (EFS) that was longer than the mean time to transplant for the BMT group (135 days). The outcome in this group was examined from the baseline time of day 135. Comparability of the BMT patients and their control group was examined for several potentially important prognostic factors and presenting features. The primary endpoint examined was EFS defined as leukemic relapse at any site or death during remission, whichever occurred first. Life table estimates were calculated by the Kaplan-Meier procedure [28]. Approximate 95% confidence intervals for EFS used Greenwood's formula [28]. Comparisons of outcome for the BMT and control group used the log rank test [29,30]. The *P*-values in the life table comparisons are based on outcome across the entire period of patient follow-up, although estimates of EFS at specific times are sometimes given for comparative purposes.

The second analysis used the data of BMT as a time-dependent covariate in the Cox proportional hazards regression [31,32]. This procedure transfers each transplant patient from the chemotherapy group into the transplant group at exactly the time in the life table that the transplant occurred for that patient. The Cox regression incorporated other factors (treatment regimen, duration of initial remission) in order to see if the general effect of transplant was altered by other variables. Estimates of the life table relative hazard rate for a particular event were calculated by the O/E method for log rank analyses and by the exponential regression coefficient method for the Cox regression [33,34].

RESULTS

There are five survivors among the 11 recipients of marrow transplants from related donors. Four patients have remained continuously free of disease, 21+ to 41+ months after transplant and one patient had a testicular relapse 11 months after transplant, was retreated, and survives free of leukemia 35+ months after transplant. Four patients died as a result of treatment-related complications; two deaths were attributed to graft-versus-host disease (1 month, 2 months), one due to idiopathic interstitial pneumonitis (3 months), and one death resulted from systemic fungal infection (4 months). Two patients had recurrent leukemia and died (12 months, 20 months). Four patients developed acute GVHD, one stage I, one stage II, and two stage IV. No patient developed chronic GVHD.

Among the seven autologous marrow recipients, there were five relapses (3–10 months after transplant). All the patients who relapsed after transplant died (3–41 months after transplant). Two autologous marrow recipients survive, free of disease, 27+ and 36+ months after transplant. There were no treatment-related deaths among the autologous recipients.

The single recipient of a matched unrelated donor

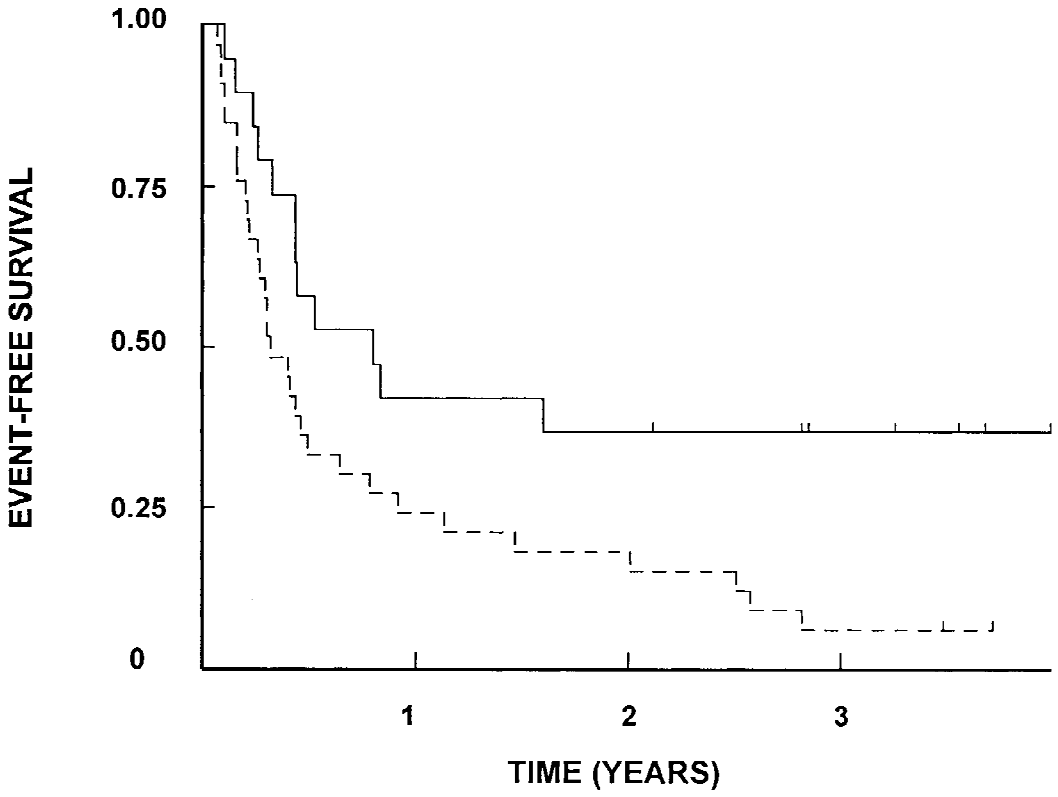

Fig. 1. Event-free survival from day of transplant (for all 19 transplanted patients, solid line), compared to chemotherapy-treated patients (n = 33, interrupted line). Day 0 for chemotherapy group is adjusted to diminish transplant bias, as described in statistical methods section. Tick marks indicate length of follow-up in patients who have not experienced an event. The difference is statistically significant ($P = 0.017$).

marrow transplant is alive and free of leukemia, 38+ months later. This patient did develop significant acute GVHD but did not develop chronic GVHD.

Estimated 24-month EFS from transplant is 37% (95% confidence interval:15–59%). The 24-month EFS of patients treated with chemotherapy is 18% (5–31%). This difference was statistically significant ($P = 0.017$; Fig. 1). Among the six chemotherapy patients alive and free of disease at 24 months, four relapsed or died in the ensuing 12 months. Among the 33 patients treated with chemotherapy, there have been 29 relapses (23 isolated bone marrow, three isolated CNS, and three bone marrow plus CNS) which occurred at a median time of 110 days. Two patients died without any evidence of prior relapse at day 37 and day 235. There are two chemotherapy patients surviving at day 1,270 and day 1,355. Among the eight surviving transplant recipients, the only event was an extramedullary relapse 11 months post-transplant. There have been no events later than 24 months after transplant.

Similar EFS was observed after related transplants and autologous transplants. Twenty-four month EFS is 33%(6–60%) for the 11 recipients of related marrow transplants, compared to 29%(0–63%) for the seven recipients of autologous transplants.

Among the patients treated with idarubicin, the EFS at 24 months was 29%(0–63%) among the seven transplant recipients, compared to 32%(11–53%) among the 19 patients treated with maintenance chemotherapy ($P = 0.69$). In contrast, among the patients treated with daunorubicin, EFS at 24 months was better among the 11 transplant recipients compared to the 13 patients who received maintenance chemotherapy (45% [15–75%] vs. 0%, respectively; $P = 0.0004$).

Fourteen transplanted patients had initial remissions shorter than 3 years; three of these patients survive, compared to four of five transplanted patients whose initial remission was greater than three years. There were 27 chemotherapy treated patients whose initial remissions were less than 3 years in duration and six chemotherapy patients with longer initial remissions; one patient in each group survives.

Multivariate analyses using the Cox proportional hazards regression model tended to confirm the results obtained by the landmark analysis method. The regression analyses showed that patients receiving transplant had an improved EFS ($P = 0.04$) with the relative event rate (RER) 2.58 times higher in the control group. Adjustment for initial chemotherapy regimen (including only randomized patients) and duration of previous remission

did not reduce the benefit of BMT ($P = 0.01$, RER = 2.59). Also, the data were consistent with possible evidence for an interaction effect of chemotherapy regimen and transplant ($P = 0.06$), where the beneficial effect of transplant was confined to the patients receiving daunorubicin. Long previous initial remission was a strong prognostic factor in the regression analysis ($P = 0.0009$) for remissions greater than 3 years compared to those less than 1 year.

DISCUSSION

Although substantial progress has been made in the primary therapy of ALL, the success of retrieval programs has not improved. As the intensity of primary therapies has escalated, this may have led not only to improved disease-free survival, but also to the adverse selection of patients who relapse, who are more likely to harbor refractory disease. Indeed, the outlook for patients who relapse is guarded, especially if that relapse occurs at a shorter interval from the time of diagnosis.

In this study, only 15% of patients had received standard therapy for low-risk disease. The remainder had received intensified therapies that incorporated features of the New York regimen [35] or the BFM protocol [36]. Prior exposure to anthracyclines limited the advisability of prolonged use of those agents in a maintenance regimen. Thus, the emphasis of this maintenance program was on high-dose cytarabine [25] and escalating dose methotrexate [24].

The efficacy of the chemotherapy maintenance regimens was clearly unsatisfactory [23], a fact made more apparent in this analysis, which excluded those patients who relapsed very early after achievement of second remission. Among the 32 patients who received chemotherapy, 2-year EFS was 18% and there are only two patients alive and disease-free at 3 years. In contrast, the transplanted patients had an actuarial survival of 37% at 2 years (Fig. 1). While the numbers of patients are small, the difference is statistically significant.

The transplanted patients represent a very heterogeneous group. Most were patients transplanted from HLA-matched related donors (n = 11). The use of transplantation for these patients was recommended by protocol; all patients who were reported to have a matched related donor and who entered second remission were transplanted. None relapsed before BMT. The selection of patients for autologous BMT (n = 7) and unrelated donor transplant (n = 1) was a decision made by individual physicians and may have involved some selection bias. There was no difference in EFS comparing matched related BMT to autologous BMT in this small patient sample. Of note, four of the six deaths after allogeneic BMT were treatment related, while all five deaths after autologous BMT were the result of leukemic relapse. In the future, use of alternate sources of hematopoietic progenitor cells, such as cord blood or T-cell depleted unrelated marrow grafts, may diminish the risk of treatment-related complications, especially GVHD [16–20,37–39].

In summary, marrow transplantation of children with ALL in second remission appeared to provide improved results, as measured by event-free survival, compared to the maintenance chemotherapy used in this study. It remains possible that less readily identifiable selection factors for which analytic correction is not possible could account for some of the difference in outcome favoring transplant. Those issues can be addressed by study designs which further limit the possibility of bias in comparisons of outcome. This smaller but more controlled trial confirms the findings of Barrett et al. from the International Bone Marrow Transplant Registry [40]. A larger randomized trial has been initiated by Children's Cancer Group (CCG) to further compare these different approaches to therapy.

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APPENDIX
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